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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/712,813	11/13/2000	Gale A. Granger	IRVN-007CON	4642

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EXAMINER
MURPHY, JOSEPH F

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/712,813	GRANGER ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- *Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.*
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- *If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.*
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-69* is/are pending in the application.

4a) Of the above claim(s) *67-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3,4,9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 43-66 in Paper No. 13, 12/19/2002 is acknowledged. The traversal is on the ground(s) that there is no burden on the Examiner to search both SEQ ID NO: 8 and 9, since both sequences were searched in the examination of Application US 00/081,385. Accordingly, claims 43-66, drawn to methods for treatment with the proteins of SEQ ID NO: 8 and 9 will be searched.

Claims 43-69 are pending. Claims 67-69 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 43-66 are under consideration.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of septic shock by administration of SEQ ID NO: 8 or SEQ ID NO: 9, does not reasonably provide enablement for: methods of treatment of arthritis or rheumatoid arthritis by administration of SEQ ID NO: 8 or 9; methods of treatment of septic shock, arthritis or rheumatoid arthritis by administration of any protein, other than SEQ ID NO: 8 or 9; methods of treatment of septic shock, arthritis or rheumatoid arthritis by administration of proteins which comprise fragments of SEQ ID NO: 8 or 9; methods of treatment of septic shock, arthritis or rheumatoid arthritis by administration of proteins which are 80% or 95% identical to

SEQ ID NO: 8 or 9; or treatment of any inflammatory disease using any protein that releases TNF receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors considered to be relevant in the instant case are set forth below:

(1) the breadth of the claims – In one embodiment, the claims are drawn to methods of treatment of arthritis or rheumatoid arthritis by administration of SEQ ID NO: 8 or 9

(2) the nature of the invention – The invention is a method of treatment of arthritis or rheumatoid arthritis by administration of a protein which cleaves and releases TNF receptor.

(3) the state of the prior art – The Gabay reference teaches that methods of treating arthritis or rheumatoid arthritis with TNF-alpha can lead to improvement of clinical and biological signs of inflammation and a reduction of radiological signs of bone erosion and cartilage destruction. However, despite these encouraging results, a significant percentage of patients do not respond to these agents, suggesting that other mediators are also involved in the pathophysiology of arthritis (page 143, column 1, third paragraph). The instant application does disclose the other mediators necessary for successful treatment of arthritis or rheumatoid arthritis by administration of SEQ ID NO: 8 or 9. The specification does not disclose that there is a nexus between the demonstrated treatment of septic shock and the treatment of arthritis or rheumatoid arthritis.

(6) the amount of direction provided by the inventor – The disclosure only teaches treatment of septic shock with SEQ ID NO: 8 or 9, but does not demonstrate the treatment of arthritis or rheumatoid arthritis by administration of SEQ ID NO: 8 or 9.

(7) the existence of working examples - Working examples are provided for TRRE of SEQ ID NO: 8 and 9, which is shown in Example 3 to alleviate septic shock (Specification at 37).

(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. As demonstrated by the Gabay reference, the treatment of arthritis or rheumatoid arthritis with novel biological agents is unpredictable. Since the claims encompass the treatment of arthritis or rheumatoid arthritis, and given the art recognized unpredictability of the treatment of arthritis or rheumatoid arthritis, it would require undue experimentation to make and use the claimed invention.

Given the breadth of claims 43-66 in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

The specification does not provide enablement for methods of treatment of septic shock, arthritis or rheumatoid arthritis by administration of any protein, other than SEQ ID NO: 8 or 9. Claims 43-66 are overly broad since insufficient guidance is provided as to which of the myriad of encompassed polypeptides that will retain the characteristics of TRRE activity. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any

experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors considered to be relevant in the instant case are set forth below:

(1) the breadth of the claims – In another embodiment, the claims are drawn to methods of treatment of septic shock, arthritis or rheumatoid arthritis by administration by administration of any protein of undisclosed structure.

(2) the nature of the invention - The instant invention is a method of treatment of septic shock, arthritis or rheumatoid arthritis by administration by administration of any protein with an undisclosed structure.

(3) the state of the prior art - The Gabay reference teaches that methods of treating arthritis or rheumatoid arthritis with TNF-alpha can lead to improvement of clinical and biological signs of inflammation and a reduction of radiological signs of bone erosion and cartilage destruction. However, despite these encouraging results, a significant percentage of patients do not respond to these agents, suggesting that other mediators are also involved in the pathophysiology of arthritis (page 143, column 1, third paragraph). The instant application does disclose the other mediators necessary for successful treatment of arthritis or rheumatoid arthritis by administration of SEQ ID NO: 8 or 9. The specification does not disclose that there is a nexus between the demonstrated treatment of septic shock and the treatment of arthritis or rheumatoid arthritis.

(6) the amount of direction provided by the inventor - Applicant has only taught the polypeptide of SEQ ID NO: 8 and 9. Applicants do not disclose any actual or prophetic examples on expected performance parameters of any other possible proteins for which no structural of functional information has been provided.

(7) the existence of working examples - Working examples are provided for TRRE of SEQ ID NO: 8 and 9, which is shown in Example 3 to alleviate septic shock (Specification at 37).

(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. As demonstrated by the Gabay reference, the treatment of arthritis or rheumatoid arthritis with novel biological agents is unpredictable. Since the claims encompass the treatment of arthritis or rheumatoid arthritis, and given the art recognized unpredictability of the treatment of arthritis or rheumatoid arthritis, it would require undue experimentation to make and use the claimed invention.

The specification does not provide enablement for methods of treatment of septic shock, arthritis or rheumatoid arthritis by administration by administration of proteins which are 80% or 95% identical to SEQ ID NO: 8 or 9. Claims 43-66 are overly broad since insufficient guidance is provided as to which of the myriad of variant polypeptides that will retain the characteristics of TRRE activity. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors considered to be relevant in the instant case are set forth below:

(1) the breadth of the claims - The claims are drawn to methods of treatment of septic shock, arthritis or rheumatoid arthritis by administration by administration of proteins which are 80% or 95% identical to SEQ ID NO: 8 or 9.

(2) the nature of the invention - The instant invention is a method of treatment of septic shock, arthritis or rheumatoid arthritis by administration by administration of proteins which are 80% or 95% identical to SEQ ID NO: 8 or 9.

(3) the state of the prior art - Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). The Voet reference demonstrates that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. (5) the level of predictability in the art - The Voet reference demonstrates the unpredictability of the protein art.

(6) the amount of direction provided by the inventor - Applicant has only taught the polypeptide of SEQ ID NO: 8 and 9. The amino acid sequence of a polypeptide determines its structural and functional properties, and predictability of which amino acids can be substituted is extremely complex and well outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible muteins of TRRE.

(7) the existence of working examples - Working examples are provided for TRRE of SEQ ID NO: 8 and 9.

(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. As demonstrated by the Voet et al. reference, it is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have

dramatic effects on the protein's function. Since the claims encompass variant polypeptides and given the art recognized unpredictability of the effect of mutations on protein function, it would require undue experimentation to make and use the claimed invention.

Given the breadth of claims 43-66 in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claims 43-66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

These are genus claims. The claims are drawn to methods of treatment of arthritis or rheumatoid arthritis by administration of SEQ ID NO: 8 or 9; methods of treatment of septic shock, arthritis or rheumatoid arthritis by administration of any protein; methods of treatment of septic shock, arthritis or rheumatoid arthritis by administration by administration of proteins which comprise fragments of SEQ ID NO: 8 or 9; methods of treatment of septic shock, arthritis or rheumatoid arthritis by administration by administration of proteins which are 80% or 95% identical to SEQ ID NO: 8 or 9. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification and claim do not place any limit

on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to SEQ ID NO: 8 or 9, and additionally encompass administration of a protein defined by a function alone i.e. cleaving and releasing TNF receptor. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the polypeptide of SEQ ID NO: 8 or 9 is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 43-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 43 is vague and indefinite in the recitation of the term "arthritic or inflammatory condition". No definition is provided for the term, and the specification does not provide sufficient guidance for the metes and bounds of the term. Claims 42-66 are rejected insofar as they depend on the recitation of the term "arthritic or inflammatory condition" in claim 43.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
March 4, 2003

YVONNE EYLER, PH.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER